MicroRNA let-7d regulates the TLX/microRNA-9 cascade to control neural cell fate and neurogenesis.

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Public Summary:
MicroRNAs are small noncoding RNAs that can affect the expression of genes. For example, microRNAs play important roles during the development of the nervous system by regulating the expression of genes involved in neurogenesis. We have found that a microRNA known as let-7d, which has been implicated in cocaine addiction and other neurological disorders, targets a gene called TLX. The protein encoded by the TLX gene is important for maintaining the self-renewal of neural stem cells; if insufficient TLX is present, neural stem cells will stop renewing themselves and will instead differentiate into mature nerve cells. Overexpression of let-7d in neural stem cells in mouse brains reduced the proliferation of these cells and led them to differentiate and migrate prematurely. This effect was similar to that seen when expression of TLX is knocked down or when microRNA-9, which is negatively-regulated by TLX, is overexpressed. We found that let-7d binds to a sequence in the untranslated region at the end of the TLX RNA (this region is known as the 3' UTR) and that let-7d reduced TLX expression levels in neural stem cells, which in turn, up-regulated miR-9 expression. Moreover, expression of both let-7d and TLX lacking its 3' UTR in neural stem cells in mouse brains restored neural stem cell proliferation. In addition, these cells did not prematurely differentiate and migrate. This suggests that, manipulating let-7d and/or genes that are regulated by let-7d could provide insight into the signaling pathways involved in the conversion and maturation of neural stem cells into neurons, which would provide a better understanding of how the brain works and could identify potential ways to improve treatment of neurological disorders.

Scientific Abstract:
MicroRNAs have important functions in the nervous system through post-transcriptional regulation of neurogenesis genes. Here we show that microRNA let-7d, which has been implicated in cocaine addiction and other neurological disorders, targets the neural stem cell regulator TLX. Overexpression of let-7d in vivo reduced neural stem cell proliferation and promoted premature neuronal differentiation and migration, a phenotype similar to those induced by TLX knockdown or overexpression of its negatively-regulated target, microRNA-9. We found a let-7d binding sequence in the tlx 3' UTR and demonstrated that let-7d reduced TLX expression levels in neural stem cells, which in turn, up-regulated miR-9 expression. Moreover, co-expression of let-7d and TLX lacking its 3' UTR in vivo restored neural stem cell proliferation and reversed the premature neuronal differentiation and migration. Therefore, manipulating let-7d and its downstream targets could be a novel strategy to unravel neurogenic signaling pathways and identify potential interventions for relevant neurological disorders.